three panels are renumbered as Figs. 9A, 9B and 9C.

ABSTRACT OF THE DISCLOSURE

Please replace the existing abstract with the one enclosed herewith.

IN THE CLAIMS

Please cancel claims 1-9.

Please add the following new claims:

--10. A purified or non-naturally occurring DNA molecule comprising a coding sequence encoding a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first reference vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

(i) a second reference vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference

vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first reference vertebrate growth hormone's receptor of a single substitution mutant of the first reference vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and

(d) a deletion of a residue found in said first reference vertebrate growth hormone but deleted in a second reference vertebrate growth hormone,

said polypeptide having growth hormone receptor antagonist activity.

11. The DNA molecule of claim 10 wherein the differences as specified in (B)(II) are solely amino acid substitutions as set forth in (a) and (b).

12. The DNA molecule of claim 11 wherein, for all non-conservative substitutions, both of conditions (II)(b)(i) and (II(b)(ii) apply.

13. The DNA molecule of claim 11 wherein all substitutions are conservative substitutions as defined in II(a).

14. The DNA molecule of claim 11, said amino acid sequence having at least about a 66% identity with the sequence of said first reference vertebrate growth hormone.

15. The DNA molecule of claim 10, said amino acid sequence having at least about a 80% identity with the sequence of said first reference vertebrate growth hormone.

16. The DNA molecule of claim 11, wherein substitutions of residues in the third alpha helix are limited to residues corresponding to bGH residues Gly119, Ala122, Leu123, Ile120, Leu116, Asp115 and Glu118.

17. The DNA molecule of claim 11, wherein the third alpha helix is at least 50% identical to the third alpha helix of said first reference vertebrate growth hormone.

18. The DNA molecule of claim 11, wherein the third alpha helix is at least 80% identical to the third alpha helix of said first reference vertebrate growth hormone.

19. The DNA molecule of claim 11, wherein the non-conservative substitutions are all of residues other than those belonging to conserved domains GD1 (hGH 9-31), GD2 (hGH 53-68), GD3 (hGH 75-93), GD4 (hGH 114-130) and GD5 (hGH 162-189).

20. The DNA molecule of claim 11, wherein the non-conservative substitutions are all of surface residues.

21. The DNA molecule of claim 11, wherein each non-conservative substitution is with a replacement amino acid found at the corresponding position in a vertebrate growth hormone, prolactin, placental lactogen, or other hormone homologous to human growth hormone, or with an amino acid which is a member of the same exchange group as an amino acid found at the corresponding position in a hormone homologous to human growth hormone.

22. The DNA molecule of claim 11, wherein each non-conservative substitution is with a replacement amino acid found at the corresponding position in a second vertebrate growth hormone, or with an amino acid which is a member of the same

exchange group as an amino acid found at that the corresponding position in a second vertebrate growth hormone.

23. The DNA molecule of claim 11, wherein each non-conservative substitution is with a replacement amino acid found at the corresponding position in a vertebrate growth hormone, prolactin, placental lactogen, or other hormone homologous to human growth hormone.

24. The DNA molecule of claim 11, wherein each non-conservative substitution is with a replacement amino acid found at the corresponding position in a second vertebrate growth hormone.

25. The DNA molecule of claim 11 in which the first reference vertebrate growth hormone is a mammalian growth hormone.

26. The DNA molecule of claim 11 in which the first ~~reference~~ vertebrate growth hormone is a human or bovine growth hormone.

27. The DNA molecule of claim 11 in which the substitution (I) is with an amino acid at least as large as proline.

28. The DNA molecule of claim 11 in which the substitution (I) is with an amino acid selected from the group consisting of Arg, Trp, Pro, Lys and Leu.

29. A purified or non-naturally occurring DNA molecule which comprise a coding sequence which encodes a polypeptide which comprises an amino acid sequence which is at least 50% identical to the amino acid sequence of a reference vertebrate growth hormone, and wherein the amino acid position corresponding to amino acid Gly 119 of bovine growth hormone is substituted with an amino acid other than alanine, said polypeptide having growth hormone antagonist activity.

30. The DNA molecule of claim 29 wherein said amino acid sequence is at least 66% identical to the amino acid sequence of ~~a reference~~ vertebrate growth hormone.

31. The DNA molecule of claim 29 wherein said amino acid

sequence is at least 80% identical to the amino acid sequence of ~~a reference~~ the first vertebrate growth hormone.

32. The DNA molecule of claim 29 wherein said amino acid sequence is at least about 90% identical to the amino acid sequence of ~~a reference~~ the first vertebrate growth hormone.

33. The DNA molecule of claim 29 wherein said ~~reference amino acid sequence~~ is human or bovine growth hormone.

34. The DNA molecule of claim 11 which has an ED50 which is less than about 10 times the ED50 of the first ~~reference~~ vertebrate growth hormone in an assay of the ability of the polypeptide to displace radiolabeled first ~~reference~~ vertebrate growth hormone from a liver membrane vertebrate growth hormone receptor.

35. A purified or non-naturally occurring DNA molecule which comprises a coding sequence which encodes a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first reference vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and either

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

(i) a second reference vertebrate growth hormone exists for which the corresponding amino

acid is a non-conservative substitution for the corresponding first reference vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first reference vertebrate growth hormone's receptor of a single substitution mutant of the first reference vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and

(b) a deletion of a residue found in said first reference vertebrate growth hormone but deleted in a second reference vertebrate growth hormone,

said polypeptide having a statistically significant inhibitory effect on the growth of transgenic mice engineered to produce said polypeptide, as compared to the growth of equivalent nontransgenic mice.

36. The DNA molecule of claim 35, wherein the ratio of the growth rate of two month old transgenic mice expressing the polypeptide, to that of their nontransgenic litter mates, is not more than 0.96:1.

37. The DNA molecule of claim 11 wherein the amino acid position corresponding to amino acid Gly 119 of bovine growth hormone is substituted with an amino acid other than proline.

38. The DNA molecule of claim 11 wherein the mutations include at least one substitution according to (II) above which

is of a residue which is part of an alpha helix of said ~~reference~~ first vertebrate growth hormone and which substitute amino acid has a greater alpha helical propensity than did the corresponding residue of said ~~reference~~ first vertebrate growth hormone.

39. The DNA molecule of claim 38 wherein said helix corresponds to the third alpha helix of bovine growth hormone.

~~40~~. The DNA molecule of claim ~~11~~ 10, further comprising a promoter operably linked to said coding sequence whereby said polypeptide may be expressed in a host cell compatible with said promoter.

41. The DNA molecule of claim 40, wherein the promoter is a regulatable promoter.

42. The DNA molecule of claim 40 which is a retroviral vector.

43. The DNA molecule of claim 40 which is a linearized DNA.

44. A cell transformed by the DNA molecule of claim 40, and which expresses said polypeptide.

45. A nonhuman transgenic animal, at least some of whose somatic and germ cells contain the DNA molecule of claim 40, and which expresses said polypeptide under promoter-activating conditions.

46. A method of preventing a condition of a human or animal subject caused by excessive growth hormone activity, or treating a condition of a human or animal subject exacerbated by growth hormone activity, which comprises administering to the subject a DNA molecule according to claim 40, under conditions conducive to the integration of said DNA into the genome of one or more cells of said subject, said subject subsequently expressing a growth hormone activity-antagonizing and pharmaceutically acceptable amount of said polypeptide, said polypeptide having growth hormone antagonist activity in said subject.

47. The method of claim 46 wherein the ~~condition is characterized by~~ mammal suffers from an excessive growth rate~~, and the antagonist has a growth-inhibitory effect~~.

48. The method of claim 47 in which the ~~condition is~~ mammal suffers from gigantism.

49. The method of claim 47 in which the ~~condition is~~ mammal suffers from acromegaly.

50. The method of claim 46 wherein the ~~condition is~~ mammal suffers from diabetes.

51. The method of claim 50 in which the ~~antagonist inhibits the development of~~ mammal suffers from diabetic retinopathy.

52. The method of claim 50 in which the ~~antagonist inhibits the development of~~ mammal suffers from glomerulosclerosis.

53. The method of claim 46 in which the ~~condition is~~ mammal suffers from hypercholesterolemia.

54. The method of claim 46 wherein the ~~condition is~~ mammal suffers from a tumor whose growth is stimulated by endogenous growth hormone.

55. The method of claim 46 in which the ~~condition is~~ mammal suffers from a tumor which secretes growth hormone.

56. The method of claim 55 in which the ~~condition is~~ mammal suffers from a tumor whose growth is stimulated by autocrine secretions of growth hormone.

57. The method of claim 46 in which the subject, prior to said administration, experienced elevated levels of growth hormone activity.

58. The method of claim 46 in which the subject, prior to said administration, experienced normal levels of growth hormone activity.

59. The method of claim 46 in which the DNA molecule is administered prenatally.

60 The method of claim 46 in which the DNA molecule is administered postnatally.

61. A method of producing a nonhuman animal which is of smaller-than-normal ~~size~~ body weight which comprises administering to the animal, before it has completed its growth, a DNA molecule according to claim 40, under conditions conducive to the integration of said DNA into the genome of one or more cells of

said animal, said animal subsequently expressing a growth hormone activity-antagonizing and pharmaceutically acceptable amount of said polypeptide, said polypeptide having growth inhibiting activity in said animal.

62. A purified or non-naturally occurring DNA molecule comprising a coding sequence encoding a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first reference vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

(i) a second reference vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first reference vertebrate growth hormone's receptor of a single substitution

mutant of the first reference vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and

(d) a deletion of a residue found in said first reference vertebrate growth hormone but deleted in a second reference vertebrate growth hormone,

(e) an insertion of a residue at an insertion point outside the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such insertion point furthermore not being between conserved residues in the vertebrate GH family, and

(e) an insertion of a residue absent in said first reference vertebrate growth hormone but present in a second reference vertebrate growth hormone,

said polypeptide having growth hormone receptor antagonist activity.--

Suite B cont.

a4 cont